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Author Present: 10:00AM–11:00AM
Hall F, West Concourse
Electrophysiology and Antiarrhythmic Drugs

H234 A NEWER CLASS III AGENT: ELECTROPHYSIOLOGIC EFFECTS IN VIVO AND IN VITRO

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H234 is an investigational compound which prolongs monophasic action potential duration in vitro. The purpose of this study was to assess the antiarrhythmic activity of H234, in vivo, in a model of sustained ventricular tachycardia induced late following infarction. H234 suppressed inducible sustained ventricular tachycardia in 3 of 12 dogs at concentrations of H234 which are being used in phase II clinical trials. This efficacy was associated with prolongation of ventricular refractoriness and electrogram QT diffusely through out the myocardium. Placebo produced no efficacy in 11 dogs. H234 did not effect ventricular conduction time or pacing threshold. To assess the potential of H234 to produce proarrhythmia 3--700 fold higher doses of H234 were infused in dogs. At 200 fold high doses no adverse effects occurred, however at 700 fold higher doses 1 of 5 dogs developed sinus arrest and asystole. No animal developed Torsade de pointes ventricular tachycardia. Conventional microelectrode studies in rabbit papillary muscle confirm that H234 (200 nM) prolonged action potential duration (90%) from 145±17 to 172±21 ms without effects on Vmax of phase zero or resting membrane potential.

The class III electrophysiologic effect of H234, is associated with antiarrhythmic activity without detectable evidence of proarrhythmia in dog.

SPONTANEOUS KENT BLOCK DURING CIRCUS MOVEMENT TACHYCARDIA DESPITE WIDE EXCITABLE GAPS AFTER CLASS IC ANTIARRHYTHMIC DRUGS

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Sustainment of orthodromic circus movement tachycardia (CMT) is considered to depend on the width of the excitable gap. The excitable gap of the Kent during CMT, expressed as time (*Kent excitable time window* -KETW-), is the CMT RR interval minus the V-A effective refractory period of the Kent (KETW CMT = RRCMT - ERPvaK). During a stimulation study, we have analyzed the relation between CMT spontaneous Kent block (SpKblk) and the KETW in 70 Pts with CMT not on antiarrhythmic drugs, in 53/70 Pts having CMT after class IC antiarrhythmic agents and in 10/70 Pts with CMT after class IA antiarrhythmics (AAD = type of antiarrhythmic drug tested).

SpKblk	AAD	n	ERPvaK	RRCMT	KETWCMT
no	no	47	250±36 }*	335±59 }@	85±57 }*
yes	no	23	283±32	321±53	38±48
no	IA	4	270±42 }*	370±35 }@	100±22 }*
yes	IA	6	293±16	337±32	43±22
no	IC	30	262±48 }*	420±74 }@	158±55 }*
yes	IC	23	327±61	405±78	78±44

(* P<0.05; @ differences not significant)

In CMT with spontaneous Kent block on class IC antiarrhythmic drugs, the slower the tachycardia rate the wider the KETW (49±29 ms in 10 CMT with an RR<400 ms & 100±39 ms in 13 CMT with an RR≥400 ms, P<0.001). Conclusions: Spontaneous Kent block during a CMT not on cardioactive agents or on IA antiarrhythmic drugs occurs with KETW that are narrower than after a IC substance (38±48 & 43±22 vs 78±44 ms, P<0.01). The development of spontaneous terminations of CMT due to retrograde Kent block despite wide excitable gaps, after IC antiarrhythmic drugs, suggests that these agents impair the conduction safety factor of the bypass tract during CMT since the activation front is far from the tail of refractoriness at the level of the Kent.

TYPE IA ANTIARRHYTHMIC DRUG EFFECT ON SIGNAL-AVERAGED QRS DURATION: RELATION TO DRUG EFFICACY

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Signal-averaged (SA) ECG characteristics are altered by antiarrhythmic (AA) drug therapy; whether drug responses at electrophysiologic testing for ventricular tachycardia (VT) can be predicted has been debated. We performed SAECG (40 Hz) at baseline and following Type I AA drug administration (10 studies in 8 patients), and compared SA-QRS duration (fQRS, msec), root-mean-square amplitude in the last 40 msec of SA-QRS (RMS, μv), and the duration under 40 μv of SA-QRS (LAS, msec). *Results*: (mean±SEM, *p<0.05) At drug study, 5 patients (Group A) had persistent but slower VT (256±19 to 351±25 msec) while 5 had no inducible VT (Group B). The fQRS was longer in Group A than Group B at baseline (135±4 vs 109±7 msec*). Group A demonstrated a greater prolongation of both fQRS (25±5 vs 9±2 msec*) and LAS (28±7 vs 3±5 msec*) than did Group B following AA therapy. Scalar surface QRS duration did not differ between groups (baseline or after AA drug). *Conclusion*: Patients with VT who respond completely to Type I AA drugs are unique in their baseline conduction on SAECG and do not require substantial conduction delay for AA drug efficacy. This suggests a greater role for other factors, such as refractoriness.

EXERCISE REVERSAL OF PROPAFENONE EFFECT IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME. DOUBLE-BLIND STUDY.

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Beta-adrenergic stimulation with isoproterenol or epinephrine has been demonstrated to antagonize the therapeutic effect of antiarrhythmic drugs in pts with Wolff-Parkinson-White syndrome (WPW), but the persistence of propafenone (P) efficacy in relation to poor-P (PPM) or extensive-P (EPM) metabolizers during a more physiologic situation such as ergometer test is unknown. Therefore, 36 symptomatic pts with WPW underwent a combined ergometer test and transesophageal stimulation in order to induce atrial fibrillation (AF) at rest (Re) and peak exercise (Ex) at the end of a week of treatment with P (900 mg/day) or placebo (Pla) given in double-blind mode. Eight pts (24%) were identified as PPM by debrisoquine test. AF inducibility (Ind), AF duration (Dur), and mean RR interval during AF (xRR; msec) was considered.

			PLACEBO		PROPAFENONE	
			PPM	EPM	PPM	EPM
Ind		Re	8(100%)	27(96%)	0(0%)	8(29%)#*
Ind		Ex	8(100%)	28(100%)	1(13%)$	13(46%)#
Dur	30 sec	Re	7(88%)	23(85%)	0(0%)	2(25%)#*
Dur	30 sec	Ex	8(100%)	28(100%)	0(0%)	6(46%)#
xRR	stress	Re	347±55	341±55	349	368±40
xRR	stress	Ex	323±41	320±43	276	331±38

#p 0.001 Pla vs P; $p 0.001 PPM vs EPM; *p 0.05 Re vs Ex.

No difference in mean work load was found between the two regimens and between EPM and PPM.

In conclusion, the data of this study indicate a reversibility of P efficacy during the ergometer test with significant difference between PPM and EPM in controlling the heart rate during AF in pts with WPW.